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(54) Title: THE SOLID ORAL PHARMACEUTICAL COMPOSITION COMPRISING A BISPHOSPHONIC ACID DERIVATIVE

(57) Abstract: Solid oral pharmaceutical composition comprising bisphosphonic acid derivative contains the cores based on a carbohydrate alcohol, preferably mannitol, uniformly dispersed in a homogenous blend of an active ingredient and excipients. The process of preparation of the above pharmaceutical formulation is also disclosed. The invention is particularly suitable to prepare solid oral dosage forms of the medicines comprising alendronic acid derivative, especially alendronic acid monosodium salt trihydrate.

The solid oral pharmaceutical composition comprising a bisphosphonic acid derivative

The present invention provides the solid oral pharmaceutical composition comprising a bisphosphonic acid derivative and the process for preparing thereof.

Bisphosphonic acid derivatives, such as clodronic, pamidronic, alendronic, risedronic acids and the salts thereof, are known to be active in calcium and phosphate metabolism mediated disorders. Alendronic acid, i.e. (4-amino-1-hydroxybutylidene)bisphosphonic acid, is taught by a German Patent specification No DE 3.016.289 (Henkel AG). Alendronic acid as monosodium salt trihydrate is an active ingredient of the pharmaceutical oral dosage form known as Fosamax, indicated for the treatment and prevention of osteoporosis. Besides the active substance this formulation comprises the following inactive excipients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium and magnesium stearate.

European Patent publication No EP 0 336 851 discloses pharmaceutical compositions containing a bisphosphonic acid derivative for oral administration, such as, but not limited to tablets, capsules, pellets, powders and dispersions. Said compositions comprise the following excipients: microcrystalline lactose and sodium lauryl sulphate, crosslinked carboxyethylcellulose and magnesium stearate, along with the active ingredient.

Solid oral dosage forms of bisphosphonic acids are also disclosed in a French Patent specification No FR 2.703.590 and in an International Patent Publication No WO 96/39410. Said forms also contain lactose.

Lactose is generally used as a filler for solid dosage forms due to its excellent compressibility, high purity and stability. However, it is known that this substance may generate formulation incompatibilities with primary or secondary amine group containing compounds. The incompatibilities are caused by the reaction between reducing aldehyde moiety of lactose and amine group present in the active ingredient, known as the Maillard reaction. The resulting degradation products decrease the therapeutic value of the drug. The formation of said products is evidenced by a brown colouring of the final drug forms. The presence of water enhance the degradation process. See e.g. Handbook of Pharmaceutical Excipients, 2nd Ed., 1994, p. 257 (ISBN 091730 60 8).

Lately, D.D. Wirth et al. have shown on the example of fluoxetine that the Maillard reaction proceeds also between lactose and secondary amines (J. Pharm. Sci. 87, 1, p. 31-39).

The molecule of alendronic acid contains a primary amine group.

The problem of browning of lactose containing solid dosage forms with alendronic acid and other bisphosphonic acid derivatives with a primary or secondary amine group was disclosed in an International Patent Publication No WO 94/12200. WO 94/12200 proposes the

method of avoiding the interaction of bisphosphonic acid derivatives comprising an amine group in the molecule with lactose by providing the dry composition of the active ingredient and excipients and the process of rpreparation thereof comprising the direct blending of said dry mix without granulation or addition of water before compression. However, the method cannot solve the instability problem of the pharmaceutical preparations during a long storage, especially in warm and dump conditions.

The object of the present invention is to provide a solid oral pharmaceutical composition of bisphosphonic acid, particularly alendronic acid or the salt thereof, characterized by the desired physicochemical properties, the adequate release rate of the active ingredient and storage stability, without any degradation of bisphosphonate and without forming of degradation products.

The object was achieved by employing as a filler a carbohydrate alcohol, preferably D-mannitol, and also by developing an internal formulation structure, which assures the uniformity of the dose, the required release rate of the active ingredient from the unit dosage form and the high stability of the final product.

One aspect of the invention is the solid oral pharmaceutical composition comprising bisphosphonic acid derivative, characterised in that it comprises the cores based on the carbohydrate alcohol, preferably the cores based on mannitol, uniformly dispersed in the blend of a bisphosphonic acid derivative and excipients.

The second aspect of the present invention is the process of preparation of the solid oral composition,

comprising the steps of forming the cores containing a carbohydrate alcohol with the addition of a disintegrant and a binder, and admixing the cores with a bisphosphonic acid derivative, lubricants and optionally with fillers, binders and/or disintegrants.

In a preferred embodiment of the invention the cores containing mannitol as a carbohydrate alcohol are formed by a wet granulation process.

Mannitol is employed to prepare many different pharmaceutical dosage forms, including also solid oral dosage forms, where it serves primarily as a filler. Mannitol, or 1,2,3,4,5,6-hexahexanol, is a hexahydroxide carbohydrate alcohol, a mannose derivative without a reducing aldehyde group in a molecule, and therefore it does not react with amine group containing compounds. Physicochemical properties of the substance, and mainly its dry and aqueous stability as well as its non-hygroscopicity, enable its use to prepare dry pharmaceutical formulations by both dry and wet granulation processes.

Instead of mannitol, the solid oral composition of the invention may comprise some other non-reducing sugar, e.g. sorbitol.

The solid oral composition of the invention may also comprise other inactive ingredients to enhance the preparation process and to render the dosage form required physical and mechanical properties, such as other diluents, among others cellulose and its derivatives, disintegrants, such as starch and its derivatives, croscarmellose, crosslinked polyvinylpyrrolidone, sodium

starch glycolate or other product based on crosslinked polymer, binders, such as polyvinylpyrrolidone, gelatin, gums of natural and synthetic origin, cellulose derivatives, e.g. hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, lubricants, e.g. sodium lauryl sulphate, magnesium stearate, as well as water soluble or insoluble colourants.

If desired, the tablets may be protected by coating, as illustrated in Pharmaceutical Dosage Forms (vol. 3), Ed. H.A. Liebermann, L.Lachmann, J.B. Schwartz (1990), Marcel Dekker Inc. New York and Basel, p. 93-125.

The preparation process of the pharmaceutical composition of the invention comprise preparing the cores containing a carbohydrate alcohol and optionally disintegrants and binders, admixing the cores with a bisphosphonic acid derivative and remaining excipients, such as binders, disintegrants, lubricants and preparing the final dosage forms.

In a preferred embodiment of the invention, the cores are formed by wet granulation of mannitol supplemented by a disintegrant, such as crosslinked polyvinylpyrrolidone, and binder, such as polyvinylpyrrolidone, the resulting granulate is rubbed through a selected screen size sieve, preferably 1 mm, dried, and, with stirring, a bisphosphonic acid derivative, such as alendronate, a lubricant (lubricants), such as sodium lauryl sulphate, magnesium stearate and other excipients are added.

The blend thus prepared is compressed to provide solid forms, such as tablets, coated tablets, dragées, or filled into hard gelatine capsules.

The solid oral dosage forms obtained from the above blend are characterised with the internal structure, wherein a homogenous mass of the active ingredient and the fillers, binders and optionally other excipients, comprise uniformly distributed core particles preferably with the diameter equal to or lower than 1 mm. The disintegrant contained in the cores causes the disintegration of the unit dosage form in an aqueous environment (in gastric juices).

Thanks to developing the above internal structure of the pharmaceutical composition of the invention, it was possible to reach desired disintegration properties of the final solid dosage form and a proper kinetics of bisphosphonic acid derivative release, as shown in the Table 1.

In the preferred embodiment, the pharmaceutical composition of the invention comprises from 3 to 60% by weight of a bisphosphonic acid derivative, from 50 to 80% by weight of mannitol, from 1.5 to 5.0% by weight of the crosslinked polyvinylpyrrolidone, from 1.5 to 3.0% by weight of polyvinylpyrrolidone, from 1.0 to 4.0% by weight of sodium lauryl sulphate and from 3.0 to 20.0% by weight of the potato starch.

Studies on physicochemical properties and stability

Tablets containing 13.05 mg of alendronic acid monosodium salt trihydrate (equivalent to 10 mg free al-

endronic acid per tablet) were stored in conditions of the accelerated ageing, in chambers at the temperature of 25°C and 60% relative humidity and in chambers at the temperature of 40°C and 70% relative humidity in the period of 12 months. Each 3 months the samples were characterised in terms of physicochemical properties and stability.

Measured parameters: the appearance of tablets, purity, alendronic acid contents and active substance release.

Analytical methods

Determination of purity:

Purity of the solid dosage form was estimated by determining the contents of a main impurity, i.e. 4-aminobutyric acid.

The determination was carried by thin layer chromatography (TLC), with the following mobile phase system: chloroform/methanol/17% ammonia (2:2:1, v/v/v) and with an immobile phase of Merck glass plates covered with silica gel G of a 0.25 mm thickness. As a developing agent a butanol solution of ninhydrine with acetic acid added was used. The size and intensity of a blot at Rf 0.5 was assessed.

The determination of active ingredient release from tablets:

The studies were carried in an apparatus for release equipped with the paddle stirrer according to the specifications of Polish Pharmacopoeia V, p. 63. The de-

termination was carried at 37°C with 50 rpm of the stirrer.

The determination of active ingredient contents in terms of alendronic acid:

The determination was carried by high pressure liquid chromatography (HPLC) on a liquid chromatograph with 250 nm length and internal diameter 4.1 mm column, packed with PRP-1 10 μm HAMILTON granulation. As a mobile phase the phosphate buffer (pH 8.0)/acetonitrile/methanol (75:20:5, v/v/v) was used with the mobile phase flow rate of 1.0 ml/min.

The investigation results for tablets determined directly after their preparation and after 12 months of storage in accelerated ageing conditions are shown in the Table 1.

Table 1. The investigation results for tablets with sodium alendronate (containing 10 mg of the active ingredient in terms of free alendronic acid), directly after the preparation and after 12 months of storage in the conditions of an accelerated ageing.

	Directly after the preparation	After 3 months		After 6 months			After 9 months		After 12 months		
		25°C 60% RH	40°C 75% RH	RT	25°C 60% RH	40°C 75% RH	25°C 60% RH	40°C 75% RH	RT	25°C 60% RH	40°C 75% RH
Appereance	White, smooth	no change	no change	no change	no change	no change	no change	no change	no change	no change	no change
Purity: below 0.1% of 4-amino-butyric acid	Below 0.1%	below 0.1%	below 0.1%	Below 0.1%	below 0.1%	below 0.1%	Below 0.1%	below 0.1%	below 0.1%	below 0.1%	below 0.1%
Alendronic acid contents in mg	9.50	9.52	9.60	9.66	9.73	9.42	9.37	9.69	9.22	9.89	9.33
Active ingredient release in %	102.0	-	100	96.0	93.6	94.0	96.3	97.0	94.6	86.3	91.8

The invention is further illustrated by the following examples without limiting the scope of the invention.

Example

Tablets with sodium alendronate at 5 mg

Tablet formulation:

Monosodium alendronate trihydrate	6.525 mg
Magnesium stearate	1.500 mg
Mannitol	79.125 mg
Crosslinked polyvinylpyrrolidone	2.930 mg
Polyvinylpyrrolidone	2.920 mg
Sodium lauryl sulphate	2.000 mg
Potato starch	5.000 mg

The method for tablet preparation

After an intimate blending, mannitol, crosslinked polyvinylpyrrolidone and polyvinylpyrrolidone were moistened with water and rubbed through a selected mesh size of 1 mm sieve. The granulate was dried at 28°C to the loss on drying of about 1.5-2.0%. With continuous stirring, the granulate was subsequently supplemented with: an active ingredient, sodium lauryl sulphate, starch, and magnesium stearate. After thorough mixing the mass was tabletted with concave punches of the diameter of 6 mm.

What is claimed is:

1. A solid oral pharmaceutical composition comprising a bisphosphonic acid derivative, characterised in that it contains the cores based on carbohydrate alcohol, uniformly dispersed in a homogenous blend of an active ingredient and excipients.

2. Composition as claimed in claim 1, characterised in that it contains mannitol as a carbohydrate alcohol.

3. Composition as claimed in claim 1, characterised in that it has a form of a dry powder.

4. Composition as claimed in claim 1, characterised in that it is formulated in unit dosage forms.

5. Composition as claimed in claim 1, characterised in that it has a form of tablets.

6. Composition as claimed in claim 1, characterised in that it contains alendronic acid monosodium salt trihydrate as a bisphosphonic acid derivative.

7. Composition as claimed in claim 1, characterised in that said included cores comprise about 50-80% of mannitol, about 1.5-5.0% of crosslinked polyvinylpyrrolidone, and 1.5-3.0% of polyvinylpyrrolidone relative to a total weight of the formulation, and said cores are surrounded with the homogenous blend of 3.0-60.0% of alendronic acid monosodium salt trihydrate, 3.0-20.0% of starch, and 1.0-4.0% of sodium lauryl sulphate, relative to a total weight of the formulation.

8. A process of preparation of the solid oral pharmaceutical composition comprising bisphosphonic acid derivative, which comprises the step of forming the cores

containing a carbohydrate alcohol with a disintegrant and a binder and combining said cores with a bisphosphonic acid derivative, lubricants and optionally fillers, binders and/or disintegrants.

9. The process as claimed in claim 8, which comprises forming cores by a wet granulation technique.

10. The process as claimed in claim 8, wherein mannitol is used as a carbohydrate alcohol.

11. The process as claimed in claim 8, wherein an alendronic acid derivative is used as a bisphosphonic acid derivative.

12. The process as claimed in claim 8, wherein alendronic acid monosodium salt trihydrate is used as a bisphosphonic acid derivative.

INTERNATIONAL SEARCH REPORT

In tional Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/66 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 29679 A (MERCK) 9 November 1995 (1995-11-09) claims 4,6,7,18	1-6
X	EP 0 421 921 A (CIBA-GEIGY) 10 April 1991 (1991-04-10) claim 1 page 3, line 5 - line 35 examples 1-3	1-4

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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